सत्यमेव जयते

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned, being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***771/Del/02*** *dated* ***25th July 2002.***

Witness my hand this 24th Day of October 2003.

CERTIFIED COPY OF PRIORITY DOCUMENT

(S.K. PANGASA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

771/D/02
25/7/02

02 AUG 2002

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5 (2), 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A METHOD FOR THE PREPARATION OF BIOAVAILABLE DOASAGE FORM OF MODAFINIL"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. ROMI BARAT SINGH
b. PANANCHUKUNNATH MANOJ KUMAR
c. VISHNUBHOTLA NAGAPRASAD
d. SUNILENDU BHUSHAN ROY
e. RAJIV MALIK

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001 – 10; 8912501 - 10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, ROMI BARAT SINGH, PANANCHUKUNNATH MANOJ KUMAR, VISHNUBHOTLA NAGAPRASAD, SUNILENDU BHUSHAN ROY, RAJIV MALIK of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. Romi Singh
(ROMI BARAT SINGH)

b.
(PANANCHUKUNNATH MANOJ KUMAR)

c. V. Nagaprasad
(VISHNUBHOTLA NAGAPRASAD)

d.
(SUNILENDU BHUSHAN ROY)

e.
(RAJIV MALIK)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **683129** dated **09.07.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **24TH** day of **July, 2002.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

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FORM 2

0771-2

25 JUL 2002

The Patents Act, 1970

(39 of 1970)

COMPLETE SPECIFICATION

(See Section 10)

A METHOD FOR THE PREPARATION OF BIOAVAILABLE DOSAGE FORM OF MODAFINIL

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a method for the preparation of bioavailable dosage form of modafinil.

Modafinil is a wakefulness-promoting agent indicated for use in narcolepsy and idiopathic hypersomnia. The exact and precise mechanism of action is not fully revealed but it is thought to modulate the central postsynaptic alpha$_1$-adrenergic receptors. Modafinil has a different pharmacokinetic profile compared to the sympathomimetic agents including amphetamines and methylphenidate.

The benzhydrylsulfinyl acetamide structure of modafinil makes it insoluble in water (<1mg/ml) and unstable at higher temperatures. Such physicochemical properties of the drug decrease its potential for abuse via injection and smoking leading to reduced cases of dependency compared to amphetamines, but at the same time makes the process of making bioavailable dosage form difficult.

The most common approach to tackle poor solubility is reduction of the drug particle size or micronization to a size of few microns. Size reduction/ micronization increase the effective exposed surface area of drug and hence the solubility. Dosage forms containing micronized drug particles no doubt enhance the solubility and consequently the bioavailability of such drugs but on the other hand it creates processing problems. Highly micronized drug particles possess poor flow properties and high chances of re-agglomeration during processing. Re-agglomeration of micronized drug particles in some cases may be so problematic that the basic concept of enhancing the solubility by increasing the effective surface area may be lost. Further, such processes require highly sophisticated and energy consuming equipment e.g. air jet mill or impact mill, which increase the overall cost of production.

It is known that the micronization of modafinil improves the dissolution in vivo, and hence its bioavailability. This approach of micronization have been highlighted in United states patent RE 37516 which discloses a pharmaceutical composition comprising a substantially homogenous mixture of modafinil particles, wherein at least about 95% of the cumulative total of modafinil particles in said composition have a diameter of less than about 200μm. On the other hand it is

preferable that not more than about 5% of the cumulative total of modafinil particles have particle sizes greater than about 200µm: it is more preferable that not more than about 5%of the cumulative total of modafinil particles have particle sizes greater than about 190µm: it is most preferable that not more than about 5% of the cumulative total of modafinil particles have particle sizes greater than about 180µm

We have now discovered a simple and cost effective method for the preparation of modafinil dosage form, which gives the desired dissolution profile and bioavailability even with >5% coarse particles of modafinil. In the present invention desired dissolution profile and bioavailability has been obtained by the addition of surface active agent or/ and a pharmaceutical carrier to modafinil by co-mixing and/or co-sifting and/or co-grinding. Addition of surface active agent and/or pharmaceutical carriers gives the desirable dissolution and bioavailability. The combination of coarse and fine particles improves the flow properties of blend and thereby facilitates processing of dosage form. The problems of re-agglomeration of fines and drug loss are taken care along with better homogeneity.

Modafinil being a water insoluble drug, preparation of bioavailable dosage form of the same is a challenging task. With the help of our novel method of co-grinding and /or co-sifting we are able to easily prepare bioavailable dosage forms of modafinil, confirmed by the convincing bioavailability results listed in Table 3.

According, the present invention relates to a method for the preparation of a bioavailable dosage form of modafinil as herein described comprising the steps of –

a. co-mixing and/or co-grinding and/or co-sifting of modafinil with surface active agent(s) and/or pharmaceutically inert carrier(s) as herein described;
b. optionally granulating the co-mix and/or co-grind and/or co-sift of step a.) as herein described;
c. optionally blending with pharmaceutically acceptable excipients as herein described;
d. compressing or filling into a suitable size dosage form as herein described; and
e. optionally coating the dosage form.

As used herein, the term "surface active agent" is referred to substances, which improve the dissolution rate by acting at the interface of the drug surface and dissolution media.

The surface active agents of the present invention may be selected from anionic, cationic or non ionic substances. Suitable anionic surface active agents include those containing carboxylate, sulfonate and sulphate ions such as sodium lauryl sulphate, sodium laurate, dialkyl sodium sulfosuccinates, particularly bis (2-ethylhexyl) sodium sulfosuccinate, sodium stearate, potassium stearate, sodium oleate and the like. Suitable cationic surfactants include those containing long chain cations such as benzalkonium chloride, bis-2-hydroxyethyl oleyl amine and the like. Suitable non-ionic surface active agents include polyoxyethylene sorbitan fatty acid esters, fatty alcohols such as lauryl, cetyl and stearyl alcohols, glyceryl esters such as the naturally occurring mono-, di- and triglycerides; fatty acid esters of fatty alcohols and other alcohols such as propylene glycol, polyethylene glycol, sorbitan, sucrose and cholesterol. Normally the surfactant is selected from solid surfactants so that it can be co-mixed and/or co-sifted and/or co-grinded with modafinil. The surface-active agent may be used in amount of about 0.2 to 10.0 percent by weight, relative to the total weight of the formulation.

Modafinil of the present invention is a mixture of coarse particles (diameter > 220µm) and fine particles (diameter < 220 µm) in the ratio of 10:90 to 25:75 by weight. Preferred mean particle size of fines is <180µm. Most preferred mean particle size of fines is 15 - 60 µm. The ratio of coarse and fine particles may vary from a value of 10:90 to 25:75 by weight. Variation within this range does not affect the dissolution profile of modafinil dosage form. Specific surface area of the total modafinil particles should be at least 0.2 m^2/gm.

As used herein, the term "pharmaceutically inert carrier" refers to a substance, which is physiologically acceptable and compatible with drug and other excipients in the formulation and has a capacity to adsorb the drug on its surface. By virtue of such adsorption, the effective surface area of the drug exposed to the dissolution media is increased manifold, which thereby increases the rate of dissolution. Such adsorption of drug on the carrier surface also prevents the re-agglomeration of drug particles due to neutralization of surface charges on the drug particles generated during milling, by an inert carrier. Carriers

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also help in wetting of drug, involving the uptake of water by capillary action, and thereby enhancing drug dissolution further. The pharmaceutically inert carrier may be used in an amount of 2% to about 25% by weight, with respect to the total weight of the formulation.

The inert carrier of the present invention can be selected from cellulose derivatives like microcrystalline cellulose, carboxymethylcellulose; silicate derivatives like magnesium silicate, colloidal silicon dioxide, magnesium trisilicate, magnesium aluminium silicate; and clays like veegum, bentonite etc.

The process of co-grinding modafinil and the solid surfactant and/or pharmaceutical carrier may advantageously be carried out in an accelerated air-jet mill or ball mill until the powder obtained is such that the mean particle diameter ≤ 60 μm. Alternatively, the drug particles with the other intragranular excipients may be granulated using granulating fluid containing dissolved surfactant. The drug can be adsorbed on to the carrier by sifting modafinil (finer fraction) with the carrier and comixing repeatedly till a uniform dispersion is formed.

The above mixture of modafinil and surface active agent and/or pharmaceutical carrier is finally formulated into oral dosage forms such as tablet, capsule etc. The excipients used may be selected from amongst diluents, binders, disintegrants, lubricants, glidants that are physiologically acceptable and compatible with modafinil and with other excipients.

Diluents of the present invention may be selected from Lactose, mannitol, sucrose, microcrystalline cellulose, starch and calcium hydrogen phosphate.

Disintegrants may be selected from croscarmellose sodium, crospovidone and sodium starch glycolate.

Binders of the present invention may be selected from starch, sugars, gums and povidone.

Lubricants of the present invention may be selected from talc, magnesium stearate, calcium stearate, polyethylene glycol, hydrogenated vegetable oils, stearic acid, sodium lauryl sulphate, sodium stearyl fumarate and sodium benzoate.

Glidants may be selected from Colloidal silicon dioxide, silicon dioxide, magnesium silicate or talc.

The present invention may be carried out by:

(i) intimately mixing and/or co-grinding and/or co-sifting the modafinil and the solid surfactant and/or the pharmaceutical carrier,

(ii) granulating with an aqueous binder solution with or without dissolved surfactant,

(iii) drying the granules ,

(iv) sifting the granules,

(v) adding lubricant to the graded granules, and

(vi) compressing to make the tablets.

Alternatively direct compression or dry granulation techniques may also be used to prepare tablets, however wet granulation process is preferred.
The tablets can be optionally coated using the standard coating processes.

The invention will be understood more clearly from the description of the Preparative Examples that follow (Table 1) and from the dissolution profile (Table 2) and bioavailability data (Table 3).

Table 1. The formulation details for Modafinil Tablets (Examples 1-6)

Ingredients (mg/tablet)						
Intragranular	**Ex. 1**	**Ex. 2**	**Ex. 3**	**Ex. 4**	**Ex. 5**	**Ex. 6**
Modafinil	30	30	20	30	30	30
Modafinil	170 (d_{90}41, d_{50}20)*	170 (d_{90}23, d_{50}12)	180 (d_{90}23, d_{50}12)	170 (d_{90}41, d_{50}20)	170 (d_{90}41, d_{50}20)	170 (d_{90}23, d_{50}12)
	**1.3344	2.1759	2.1759			
Colloidol silicon dioxide	10	20	20	10	20	20
Sodium Lauryl sulphate	-	-	-	4	-	4
Polysorbate 80	-	-	-	-	5	-
Lactose	122	112	112	122	112	112
Starch	125	125	125	125	125	125
Croscarmellose Sodium	10	10	10	10	10	10
Povidone	10	10	10	10	10	10
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Extragranular						
Croscarmellose Sodium	10	10	10	10	10	10
Colloidal silicon dioxide	5	5	5	5	5	5
Talc	5	5	5	5	5	5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5

*d_xy represents x% of particles with diameter ≤y μm.
** Specific surface area of total modafinil particles in m^2/gm.

Table 2. Dissolution profile of the modafinil tablets of the present invention prepared as per Examples 1-6, carried out in the USP Apparatus II, 900ml, 25 rpm, water (values are indicated in cumulative percent release)

Time	Ex.1	Ex.2	Ex.3	Ex.4	Ex.5	Ex.6
15 min	34	44	42	36	38	45
30 min	37	56	57	40	41	56
45 min	41	59	69	45	45	64
60 min	42	63	72	47	47	67
90 min	47	69	75	51	51	71

Table 3: Bioavailability data (in 12 volunteers)

Dosage Form	T_{max}	C_{max}	AUC $_{(0-\infty)}$
Tablets prepared as per Ex.3	3.63+4.04	3.91+0.59	67.82+45.14

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WE CLAIM:

1. A method for the preparation of a bioavailable dosage form of modafinil as herein described comprising the steps of –
    a. co-mixing and/or co-grinding and/or co-sifting of modafinil with surface active agent(s) and/or pharmaceutically inert carrier(s) as herein described;
    b. optionally granulating the co-mix and/or co-grind and/or co-sift of step a.) as herein described;
    c. optionally blending with pharmaceutically acceptable excipients as herein described;
    d. compressing or filling into a suitable size dosage form as herein described; and
    e. optionally coating the dosage form.

2. The method according to claim 1 wherein about 10%-25% of modafinil particles by weight have diameter > 220µm and about 90%-75% of modafinil particles by weight have diameter < 220µm.

3. The method according to claim 2 wherein about 10% of modafinil particles by weight have diameter > 220µm and about 90% of modafinil particles by weight have diameter < 220µm.

4. The method according to claim 2 wherein about 15% of modafinil particles by weight have diameter > 220µm and about 85% of modafinil particles by weight have diameter < 220µm.

5. The method according to claim 2 wherein about 25% of modafinil particles by weight have diameter > 220µm and about 75% of modafinil particles by weight have diameter < 220µm.

6. The process according to claim 1 wherein the specific surface area of the total modafinil particles is at least 0.2 m^2/gm.

7. The method according to claim 1 wherein the surface active agent is anionic, cationic or non ionic.

8. The method according to claim 7 wherein the anionic surface active agents include sodium lauryl sulphate, sodium laurate, dialkyl sodium sulfosuccinates, sodium stearate, potassium stearate, sodium oleate, and the like.

9. The method according to claim 8 wherein the anionic surface active agent is sodium lauryl sulphate.

10. The methods according to claim 7 wherein the cationic surfactants include benzalkonium chloride, bis-2-hydroxyethyl oleyl amine, and the like.

11. The method according to claim 7 wherein the non-ionic surface active agents include polyoxyethylene sorbitan fatty acid esters, fatty alcohols, glyceryl esters, fatty acid esters of fatty alcohols and other alcohols.

12. The method according to claim 11 wherein the fatty alcohols are lauryl, cetyl and stearyl alcohols.

13. The method according to claim 11 wherein the glyceryl esters are the naturally occurring mono-, di- and triglycerides.

14. The method according to claim 11 wherein the other alcohols are propylene glycol, polyethylene glycol, sorbitan, sucrose and cholesterol.

15. The method according to claim 11 wherein the non-ionic surface active agent is polysorbate.

16. The method according to claim 1 wherein the amount of surface active agent is about 0.2 to 10% by weight, relative to the total weight of the formulation.

17. The method according to claim 1 wherein the pharmaceutically inert carrier is selected from the group consisting of cellulose, silicate derivatives and clays.

18. The method according to claim 17 wherein the cellulose derivative is microcrystalline cellulose, carboxymethylcellulose and the like.

19. The method according to claim 17 wherein the silicate derivative is magnesium silicate, colloidal silicon dioxide, magnesium trisilicate, magnesium aluminium silicate and the like.

20. The method according to claim 17 wherein clay is veegum, bentonite and the like.

21. The method according to claim 1 wherein amount of pharmaceutically inert carrier is about 2% to 25% by weight, relative to the total weight of the formulation.

22. The method according to claim 1 wherein surface active agent and /or pharmaceutically inert carrier is co-grinded with modafinil.

23. The method according to claim 1 wherein the dosage form is a tablet or a capsule.

24. The method according to claim 23 wherein the dosage form is a tablet.

25. The method according to claim 24 wherein the tablet comprises other pharmaceutically acceptable excipients in addition to modafinil, surface active agent (s) and/or pharmaceutically inert carrier(s).

26. The method according to claim 25 wherein the other pharmaceutically acceptable excipients are selected from the group consisting of diluents, binders, disintegrants, lubricants and glidants.

27. The method according to claim 1 wherein granulation of the co-mix and/or co-grind and/or co-sift is carried out by the process of wet granulation.

28. The method according to claim 1 wherein granulation of the co-mix and/or co-grind and/or co-sift is carried out by the process of dry granulation.

29. The method according to claim 23 wherein the dosage form is a capsule.

30. A method for the preparation of a bioavailable dosage form of modafinil comprising the steps of –

a. co-mixing and/or co-grinding and/or co-sifting of modafinil with surface active agent(s) and/or pharmaceutically inert carrier(s);
b. optionally granulating the co-mix and/or co-grind and/or co-sift of step a.);
c. optionally blending with pharmaceutically acceptable excipients;
d. compressing or filling into a suitable size dosage form; and
e. optionally coating the dosage form

substantially as described and illustrated in the examples herein.

Dated this **24TH** day of **July, 2002.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

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ABSTRACT

A METHOD FOR THE PREPARATION OF BIOAVAILABLE DOSAGE FORM OF MODAFINIL

The present invention relates to a method for the preparation of bioavailable dosage form of modafinil.